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ADRENALINE-TYPE ARTERIOSCLEROSIS INDUCED BY EXPERIMENTAL COARCTATION OF THE AORTA IN RABBITS

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The study of the so-called coarctation of the aorta may offer data even to the much discussed relation of hypertension and arteriosclerosis. The narrowed segment of the aorta situated closely below the attachment of the ligamentum arteriosum divides the vascular tree into two parts and accordingly marked differences in systolic blood pressure are obtained if measured on both the upper and lower extremities (BROWN, 1934, and others). In three cases of coarctation of the aorta recently autopsied in this Department, despite the young age (20, 34 and 42 years old males) fairly grave and extensive arteriosclerosis was noted in the arteries of the upper body while such changes in the abdominal aorta and in the arteries of the lower body were either completely absent, or only slight (ORMOS and SZTANOJEVITS, 1954). These post mortem observations have made it worth while to investigate the problem by means inducing coarctation of the aorta in animals.

Methods

The experiments were made on male and female rabbits, weighing more than 2 kg. each. They were less than 1 year of age, but their exact ages were not known. The rabbits were of hybrid strain (Belgian-Viennese crossbreed). Their diet consisted of mixed green herbage (chiefly clover) and oats; water was not restricted.

As the rabbits could poorly withstand thoracotomy, the aorta was exposed in the retroperitoneal space below the diaphragm through a paravertebral approach under light ether anaesthesia and aseptic conditions. The stenosis has been for the most part established above the origin of the coeliac axis, in some cases closely below it, by means of a clip consisting of a zinc band 4 mm. wide and bent in „U" form over the circumference of the aorta.

Some of the rabbits thus operated died soon after the operation. Altogether 12 rabbits survived 14 days following operation. 7 of the 12 rabbits died spontaneously and 5 were sacrificed by air-embolism 16 to 48 days after operation. Complete autopsy was made in all cases, thereafter both the aorta with its larger branches and the visceral organs have been fixed in 4 per cent formaldehyde. Autopsy of the spontaneously died animals revealed bronchopneumonia in four cases; in one empyema was present. In the other two animals gross examination did not yield any satisfactory explanation as to the cause of death.

The blood pressure in the auricular central artery had been measured several times both pre- and postoperatively by means of the Grant and Rothschild apparatus. For comparison and to recognize the incidence of eventual spontaneous vascular changes, the aorta of non-operated rabbits of the identical strain of the same age and kept on the same diet and under the same laboratory conditions has been examined. No vascular lesions whatsoever could be noted in any case.

Parts of the aorta below and above the narrowed segment, its larger branches and the visceral organs were histologically examined. Blocks were embedded in paraffin. All sections were stained as a routine with haematoxylin and eosin, by van Gieson's method, with orcein, resorcine-fuchsin and cresyl violet, and Kossa's calcium reaction has also been carried out. Frozen sections were also made from the vessels ; these were stained with Sudan III.

Results

A slight elevation in blood pressure could be observed in ten rabbits surviving the 14th day after operation, while no change occurred in the blood pressure of two animals. Before operation the mean blood pressure of these ten rabbits was 77,9 $\pm$ 4,8* mm mercury. In some cases the blood pressure rose to 135 mm mercury a few days after the operation (Table I) ; a higher value was obtained in no case. After the operation the mean blood pressure of the ten rabbits was 115 $\pm$ 6,7* mm mercury.

Table I

Ref. no.	Survival time in days	Blood pressure before operation	Blood pressure after operation	Severity of aortic changes
1.	16	91	135	++
2.	20	50	70	+++
3.	21	62	130	+++
4.	23	80	95	++
5.	24	64	100	+++
6.	25	88	128	+
7.	30	80	110	+++
8.	36	90	70	−
9.	37	97	125	++
10.	37	92	135	+
11.	38	75	122	+++
12.	48	72	72	−

Gross vascular lesions. In the aorta of all the rabbits without any exception in which blood pressure was elevated after the operation, very remarkable changes could be noted even by the naked eye. The severity of the aortic changes was variable ; in 5 rabbits multiple aneurysms developed, associated with very severe sclerotic phenomena. In 4 rabbits the aortic dilatations of 5—10 mm in diameter were confined to the aortic arch, the descending and thoracic aorta,

* Standard error.

i. e. to the portion of the aorta above the stenosis (Fig. 1), in one animal a few smaller aneurysms developed also immediately below the constriction. The dilatations were located fairly close to each other, their walls were parchmentlike, thinned, hard but fragile to slight pressure with an „egg-shell crackling". In two rabbits hard, scutum-like plaques, measuring from 1—2 mm. to several centimetres in diameter developed without any definite dilatations. Calcification of the

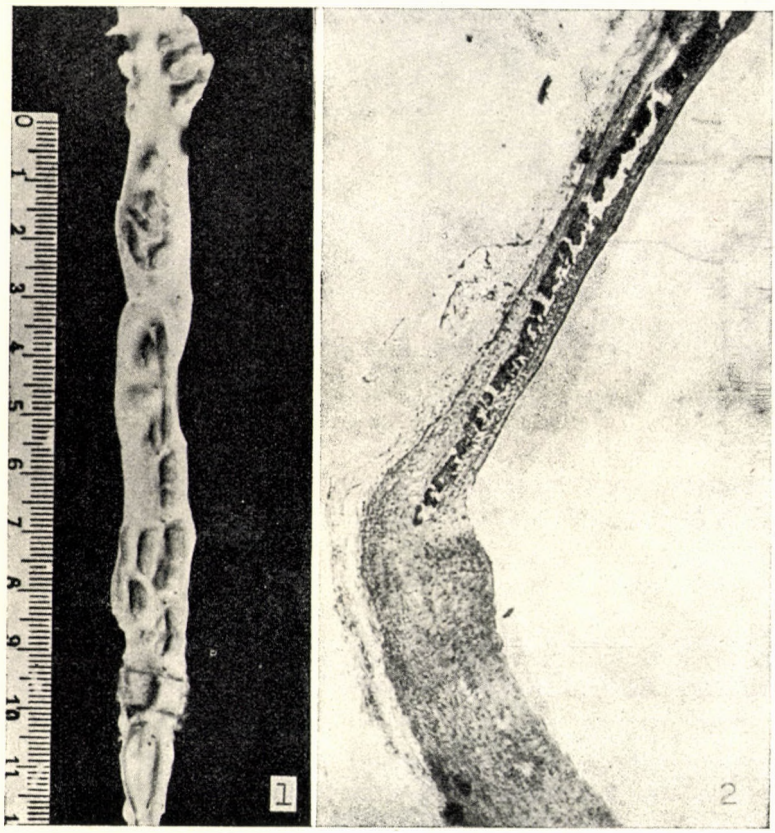

Fig. 1. Aorta of rabbit killed on 38th day. Several aneurysms with calcified wall above the stenosed part
Fig. 2. Aorta of rabbit died on 20th day. ×55. In the upper part thinning of the wall and calcification of the media can be seen

aortic wall was noted in 7 rabbits and in the thoracic and descending aorta of the three other animals the intima became focally uneven, forming a slight vaulting of the aortic wall in some places. The colour of the intima in the hardened or dilatated spaces was hardly differing from that of the intact portions ; yellow, fatty patches were seen in no case.

Microscopical vascular lesions. In all the rabbits, lesions of the aortic media of variable severity could be noted. Light focal lipoidosis of the intima was

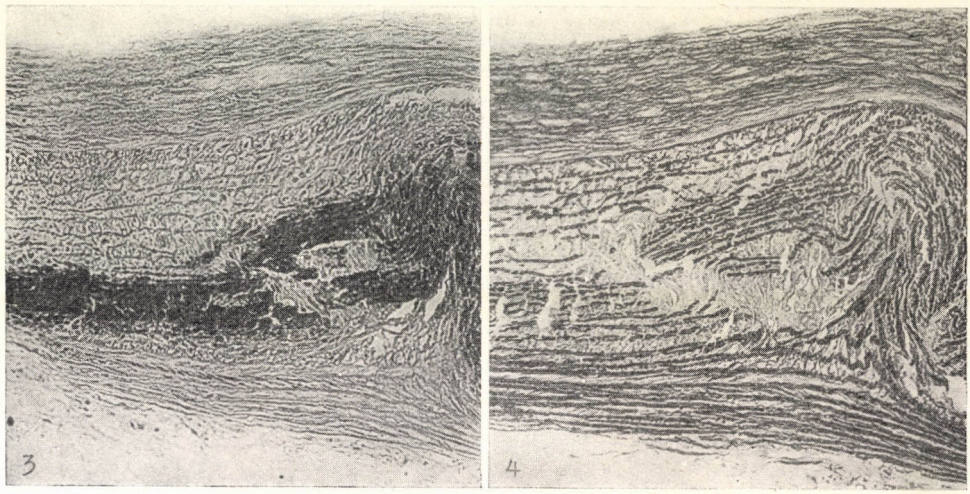

Fig. 3. Same rabbit as in Fig. 1. Kossa's stain, ×175
Fig. 4. Same portion of aorta, same magnification as in Fig. 3. with orcein stain. The elastic fibres in the media are fragmented

Fig. 5. Aorta of rabbit killed on 25th day. Foci consisting of mucoid substance in the media Haematoxylin eosin stain, ×175

present only in one case (in the rabbit died on the 37th day), accompanied by severe medial changes. Along the dilated segment the aortic wall was thinned due to narrowing of the media. All over the dilated area the media stains almost

in all its thickness a uniform dark blue with haematoxylin, suggesting deposits of limesalts (Fig. 2). CAMERON (1930) stated that haematoxylin stains not the lime itself but the basic substance in which lime salts precipitate. The calcification in the media was proved by the Kossa-reaction, too (Fig. 3). Elastic fibres could

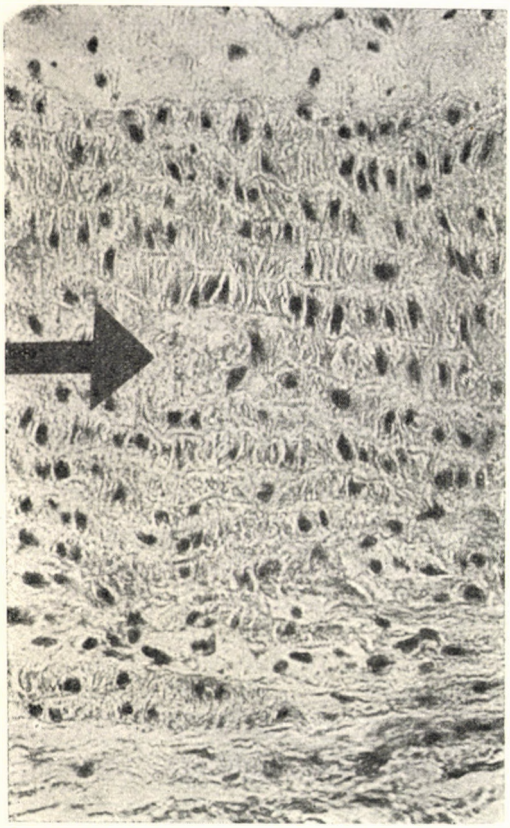

Fig. 6. Rabbit killed on 37th day. Fine calcareous granules in the media (marked with arrow), haematoxylin eosin stain, ×350

be for the most part demonstrated in the area of the calcification ; they were, however, not wavy but straightened and closely packed. The extended elastic fibres often became fragmented (Fig. 4). Muscular elements, however, were absent in the calcareous foci. In the immediate vicinity of the calcareous foci, accumulation of fibroblasts sometimes occurred, with slight formation of collagen fibres.

Noteworthy are the early i. e. the mild changes in the aorta. Small foci appearing in the media may be considered as the earliest changes demonstrable with the methods employed in our experiments. These often spindle shaped foci stain pale-blue with haematoxylin, while with cresylviolet, recommended by

MERKEL, they give metachromatic staining. The mucoid character of such substances appearing in the aortic wall in connection with arteriosclerosis was first recognised by BJÖRLING (1911). They appear in general between two elastic fibres pushing them somewhat apart (Fig. 5), and simultaneously degeneration

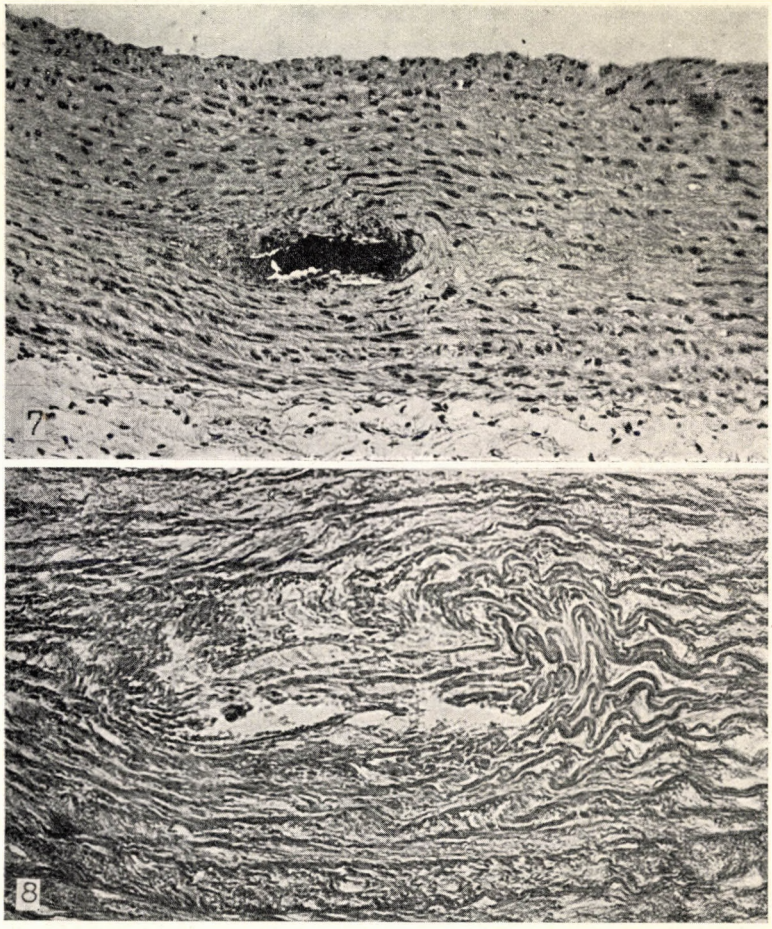

Fig. 7. Rabbit died on 23rd day. Small calcareous focus in the media, ×175
Fig. 8. Same as Fig. 7. Orcein stain, ×350

of muscular elements can be observed. In some of the small foci, formed in the media, there is fine fragmentation of the elastic fibres and small calcium salt granules appear (Fig. 6). In other areas small granules of lime salt appear on the surface of seemingly intact elastic fibres. Completely calcified small foci in the media can already be considered as an advanced change (Fig. 7). The elastic fibres on their edge become strikingly wavy, in the focus itself, however, they are straight and frequently fragmented (Fig. 8).

On the basis of the histological findings the development of the changes in the aorta can be divided into three stages. 1. Appearance of mucoid substance in small foci and degeneration of muscular elements, 2. splitting of elastic fibres and appearance of small calcium-salt granules, 3. extensive calcification of the media and consequent dilatation of the lumen due to stretching.

No particular changes have been noted in other organs with the routine staining methods employed.

The results of the experiment are shown in Table I. It is clear from the data that there is no correlation between the severity of the aortic changes produced and the survival time of the rabbits. The most severe aortic sclerosis has been found in the animals surviving 21, 24 and 38 days, while the mildest one in those surviving 25 and 37 days. Though, as already mentioned, changes in the aorta developed exclusively in rabbits whose blood pressure was slightly elevated following operation. Nevertheless, there seems to be no correlation between the severity of the aortic sclerosis produced and the rate of blood pressure elevation. As to the effect of elevated blood pressure and of the aortic sclerosis on the heart, although the weight of the heart was fairly variable in the single rabbits, the mean heart weight of 9 rabbits with elevated blood pressure was 10,7 gr., more than 35 per cent higher than that of the controls of identical body weight (7,8 gr.).

Discussion

The changes in the aorta induced by experimental coarctation correspond to that form of experimental arteriosclerosis which is generally known as adrenaline-type sclerosis. Its histological picture has been first studied by ERB (1905), B. FISCHER (1905), SCHEIDEMANDEL (1905), and K. ZIEGLER (1905). According to B. FISCHER, the initial change consists in necrosis of the smooth muscle fibres of the media, followed by fragmentation of the elastic fibres and calcification. ZIEGLER (1905) and KLOTZ (1906) were the first to compare experimental adrenaline sclerosis with the medial calcification in humans described by MÖNCKEBERG (1903). Adrenaline-type arteriosclerosis is somewhat similar to the medial calcification of human aorta described by BLUMENTHAL et al. (1944).

Since JOSUÉ (1903) had produced medial calcinosis in the aorta of rabbits by intravenous adrenaline injections, the same change was induced by a variety of substances, such as nicotine (ADLER and HENSEL, 1906); irradiated ergosterine (KREITMAIR and MOLL, 1928, VANDERVEER, 1931, DUGUID, DUGGAN and GOUGH, 1932); vitamin D (HARRISON, 1933); thyroid gland (B. FISCHER, 1905); thyroxine (KAGAWA, 1933, BALÓ, 1939); vasopressin (BYROM, 1937); angiotonin (PAGE, 1940); ammonium hydroxide (BALÓ, 1938); and other substances.

The mechanism underlying the effect of these substances, which all induce the same change in the arterial wall, is still under discussion. JOSUÉ (1903)

attributed to adrenaline an elective toxic effect exerted on the arterial wall beside that of raising arterial pressure. WATERMAN (1908) suggested three pathogenetic factors, viz. elevated blood-pressure, chemical effect exerted on the arterial wall and contraction of the vasa vasorum. BRAUN (1905), and later KLOTZ (1906), inhibited the adrenaline induced elevation of blood pressure by amyl nitrite or nitroglycerine, nevertheless aortic sclerosis developed. KREMER, WRIGHT and SCARFF (1933) produced hypertension in rabbits by bilateral extirpation of the aortic and sinus nerves and saw arterial lesions essentially of the adrenaline-type to develop. In BALÓ's opinion (1938), acidosis is the common factor in the effect of the different substances. HUEPER's (1944) conception of arteriosclerosis may be applied also to the adrenaline-type sclerosis. Thus the vascular changes were sequels of vascular spasm: HUEPER assumed that prolonged spasm produces anoxia in the muscular coat; this would be then followed by degeneration, necrosis and, finally, calcification.

A study of the relation of hypertension and arteriosclerosis by employing various chemical agents is rendered difficult by the fact that a complex mechanism set forth by these agents has to be taken into account. The problem seems to be more easily approachable if the elevation in blood pressure is induced mechanically. HARVEY (1909) compressed the abdominal aorta of rabbits through the abdominal wall daily for three minutes; in this way he was able to produce hypertension in 46 days, with extensive calcification all over the thoracic aorta. As far as we know, surgical narrowing of the aorta has been used only by DILL and ISENHOUR (1942), who successfully induced changes in the aorta. In rabbits fed a diet containing a known amount of cholesterin (0,2 per cent), they constricted the aorta above the origin of the renal arteries, and induced in this way cholesterin-type intimal changes in the thoracic aorta of 7 out of 15 rabbits, whose blood pressure was constantly above 140 mm mercury. Plaque formation seemed to be proportional to the severity and duration of the blood pressure elevation.

The results of our above described investigations differ from those of DILL and ISENHOUR, although we constricted the aorta at about the same place as they did. First of all, in our experiments arteficial coarctation has failed to increase considerably the blood pressure. According to TIGERSTEDT (1922), the mean systolic blood pressure of the rabbit is 100 mm mercury, varying from 80 to 120 mm. SCARFF (1927), employing VAN LEERSUM's (1911) carotid loop method, found an average pressure of 95 mm. KREMER, WRIGHT and SCARFF (1933) found the average resting blood pressure of rabbits at about 100 mm. GRANT and ROTHSCHILD (1934) estimated the normal range to between 70 and 91 mm, with their own apparatus. Since the mean blood pressure of our rabbits, as measured with Grant and Rotschild's apparatus, was found to be 78 mm, the mean value of 115 mm obtained after operation means only a slight elevation in blood pressure. In spite of this, very severe changes developed in the aorta

within a short period, namely an adrenaline-type medial calcification in each case. Accordingly, no correlation seemed to exist between the severity of changes produced in the aorta and the rate of blood pressure elevation.

The question may be raised, how far spontaneous sclerosis of the aorta has to be taken into consideration in rabbits. The problem has been thoroughly studied by DOMINGUEZ (1928) who found that the frequency of aortic calcinosis varies regionally, in some places it is rare or missing, but is frequent elsewhere. In his opinion, derived from data of 3,500 rabbits, the incidence is under 6 per cent ; he has however, emphasized that severe changes are very rare (less than 0,3 per cent). NUZUM, ELLIOT, EVANS and PRIEST (1930), examining 190 normal rabbits 2 to 3 years old, found arteriosclerosis in 5,8 per cent. MAEGRAITH and CARLETON (1939), on the other hand, observed gross changes in the aorta in 45 rabbits from among 144. These animals had, however, been previously used in different experiments, aiming partly at elevation of blood pressure. As the rabbits in our experiments were young, below one year of age, and because in Hungary spontaneous sclerosis of the aorta is rare, even in older rabbits, the changes observed must be considered as sequels of the coarctation of the aorta established surgically. Infection of some kind seems out of question ; only one rabbit died in thoracic empyema ; its aorta, however, was quite intact.

From the present experiments it may be concluded that in the rabbit elevation of blood pressure, however slight, plays an important role in the pathogenesis of arteriosclerosis developing after experimental coarctation of the aorta. Our investigations in progress may reveal the possible role of other (hormonal, humoral, neural) causative factors. The mechanism of hypertension following coarctation of the aorta has not been elucidated either. TEMESVÁRI, ÁDÁM, KESZLER and LITTMANN (1953) induced permanent hypertension in both the upper and lower parts of the body of dogs by narrowing the thoracic aorta ; in their opinion the renal pressor mechanism has no primary role in this form of experimental hypertension.

BLUMENTHAL, HANDLER and BLACHE (1954) made recently the remarkable statement that arteriosclerosis is fundamentally an adaptive, structural as well as biochemical, response to mechanical factors. The Hungarian pathologist GENERSICH (1899) had assumed essentially the same 55 years before.

Summary

The relation between coarctation of the aorta and arteriosclerosis has been experimentally studied on the basis of the post mortem observation made in man that severe arteriosclerotic changes occur merely above the stenosed part. Narrowing of the aorta has been brought about in rabbits by placing a metal clip above the origin of the coeliac artery. In 10 of the 12 rabbits surviving the 14th day after the operation, moderate elevation of blood pressure, and in all these animals an adrenaline-type aortic sclerosis of variable degree occurred. Severe medial calcification associated with aneurysms appeared as early as after three weeks, limited, however, for the most part to the portion of the aorta above the stenosis. There was seemingly no relation between the severity of aortic sclerosis and the rate of blood pressure elevation.

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ВЫЗЫВАНИЕ АРТЕРИОСКЛЕРОЗА АДРЕНАЛИНОВОГО ТИПА У КРОЛИКОВ ОПЕРАТИВНЫМ СОЗДАНИЕМ COARCTATIO AORTAE

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Авторы экспериментально исследовали связь между coarctatio aortae и артериосклерозом, исходя при этом из своих наблюдений, сделанных около секционного стола, согласно которым при coarctatio aortae тяжелые артериосклеротические изменения возникают только выше сужения аорты. Авторы создали у кроликов выше отхождения чревной артерии сужение аорты, путем наложения металлической скобы. На 14 день после операции у 10 из выживающих 12 кроликов было обнаружено умеренное повышение кровяного давления, и у них без исключения образовался различной степени артериосклероз аорты адреналинового типа. Тяжелое обызвествление средней оболочки с образованием аневризм возникло уже через 3 недели, причем оно ограничивалось в большинстве случаев на части аорты выше сужения. Между степенью вызванного артериосклероза и размером повышения кровяного давления, повидимому, не существует связи.

EXPERIMENTELLE ARTERIOSKLEROSE VOM ADRENALINTYPUS BEIM KANINCHEN NACH OPERATIVER ERZEUGUNG EINER AORTENKOARKTATION

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Ausgehend von ihren am Sektionstisch gemachten Beobachtungen, laut welchen bei Coarctatio Aortae schwere arteriosklerotische Veränderungen nur oberhalb der Verengung vorkommen, haben die Autoren den Zusammenhang der Aortenkoarktation und der Arteriosklerose experimentell untersucht. An Kaninchen wurde oberhalb der Ausgangsstelle der A. coeliaca durch Anbringung einer Metallklammer eine Aortenverengung hervorgerufen. Am 14. Tage nach dem Eingriff haben die Autoren an 10 von den überlebenden 12 Kaninchen eine mässige Steigerung des Blutdrucks festgestellt, und an diesen Tieren entwickelte sich ausnahmslos eine Arteriosklerose verschiedenen Grades vom Adrenalintypus. Bereits nach drei Wochen entstand eine Mediaverkalkung mit Bildung von Aneurysmen, die in der Mehrzahl der Fälle sich auf die Aortenteile oberhalb der Verengung beschränkte. Zwischen dem Grad der hervorgerufenen Arteriosklerose und dem Ausmass der Blutdrucksteigerung scheint kein Zusammenhang zu bestehen.

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